REMARKS

Claims 1-5, 6-32, and 44-71 are pending. Claims 1, 10-12, 14, 16, 17, 31, 32, and 44 have been amended and claims 6, 7, and 33-42 have been canceled. Claims 53 – 71 have been newly added. Support for the amendments is found throughout the specification as originally filed. Applicants respectfully submit that no new matter is presented thereby. Entry of the amendments is respectfully requested.

Applicants hereby affirm the election of Group I, claims 1-32 and 44-52 made during a telephonic interview with the Examiner on April 11, 2002. Claims 33-42 have been canceled.

The Examiner has stated that the Oath/Declaration is defective as not including the post office address of each inventor. Applicants respectfully submit that this information is provided on the Declarations as filed. The Examiner is requested to clarify what information is missing.

Claims 1-3, 6-15, 17,18, 20-22, 27-30, 32, and 44-52 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5, 7-23, 25, 27, 28-30, 34-37, and 41-45 of copending application Serial No. 09/568,818. Applicants respectfully submit a timely response will be filed upon allowance of claims.

Claims 10-14, 43, and 49 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite. Claims 10-12 and 14 have been amended to replace "surfactant" with the term "phospholipid", which finds proper antecedent basis in claim 1. Thus, Applicant respectfully submits that this rejection has been overcome. Regarding claim 43, Applicants respectfully request the Examiner renumber the claims as the claims have been misnumbered.

As set forth in the Examiner Interview Summary of August 9, 2002, claims 1-32 and 44-52 have been rejected under 35 U.S.C. §103 as being obvious over Hanes et al. in view of Materne et al. and Edwards et al. As stated by the Examiner, it would have been obvious to substitute the calcium phosphatidylcholine of Materne for the phospholipid of Hanes et al. because Materne et al. discloses that calcium phophatidylcholine is processed

more readily than pure phosphatidylcholine and that powder or granular products containing calcium phosphatidylcholine have increased stability. The Examiner further states that it would be obvious to make the particle porous in view of the beneficial aerosolization properties disclosed in Edwards et al.

Claims 1, 32, 44 and 59 recite saturated phospholipids. A preferred embodiment of the present invention is directed to saturated phospholipids, as disclosed for example at page 9, lines 1-17. Applicants also submit herewith the declaration of Dr. Jeffry Weers under 37 C.F.R. §1.132 relating the unexpected results attributed to the use of metal ions such as calcium on the properties, such as physical stability, on the phospholipid compositions of the present invention. Applicants respectfully submit that this rejection has been overcome for the reasons that follow.

Hanes et al. is directed to large, light particles suitable for pulmonary administration. Phospholipids such as DPPC and DSPC are suitable for the matrix material of the particulates. Hanes et al. does not disclose or suggest the use of metal ions such as calcium in the particulate formulations.

Materne et al. is directed to a high purity calcium phosphatidylcholine chloride bulk product which may be converted to pharmaceutical preparations. The phospholipids of Materne et al. are extracted from lecithin. As seen in Materne et al. (1:32+), such materials suffer from various disadvantages. For example, such materials are obtained as a plastic material having low stability which makes it hard to process and handle (1:40-41). Such disadvantages are understood by one of ordinary skill in the art to relate to issues related to chemical stability of unsaturated phospholipids. Thus, Materne et al. is directed to overcoming issues related to chemical stability of unsaturated phosphatidylcholines.

The focus of Materne et al. on chemical stability is further evidenced at page 1, lines 95-101 wherein it is stated that the calcium phosphatidylcholine chloride of the Materne et al. invention is of high purity. This disclosure read in the context of the background disadvantages of such phospholipid materials makes it clear to one of ordinary skill in the art that the invention of Materne et al. is directed to overcoming issues related to chemical stability. Materne et al. discloses that the calcium

phosphatidylcholine chloride of that invention may then be further processed into pharmaceutical preparations, based on its usefulness as a nutritive.

The present invention is directed, at least in part, to the unexpected findings as to the enhanced physical stability and dispersibility of phospholipid formulations containing a metal ion-lipid complex. Such physical stability is extremely important in the case of pharmaceutical products, which must remain storage stable throughout their shelf-life. Physical stability is also of particular importance to particulates intended for pulmonary administration as such particulates must be highly dispersible and maintain satisfactory aerosol performance, as measured by their geometric and aerodynamic diameters, for example.

The Examiner states that it would be obvious to substitute the calcium phosphatidylcholine of Materne et al. for the phospholipid of Hanes et al. Such a combination would not result in the formation of the highly dispersible or storage stable dry powders as claimed. As discussed above, Materne et al. discloses the use of an unsaturated phospholipid in producing the calcium phosphatidylcholine compositions disclosed therein. This interpretation of Materne et al. as teaching unsaturated phospholipids is discussed in paragraphs 5 and 6 in the declaration submitted herewith. Unsaturated phospholipids are cohesive, plastic and poorly dispersible and thus are not suitable for use as storage stable dry powder pharmaceuticals or pulmonary applications as claimed. This is further described in paragraph 7 of the attached declaration. Thus, the substitution proposed by the Examiner would not result in the invention as claimed.

In addition, claim 31 is directed to phospholipid/metal ion complexes wherein the gel to liquid crystal transition temperature exceeds the composition storage temperature by at least 20 °C. As seen in paragraphs 4, 7, and 17 of the declaration and discussed below, the materials of Materne et al. exhibit a gel to liquid crystal transition temperature of below O °C, even with the addition of metal ions. Therefore, Materne et al. does not disclose or suggest such storage stable phospholipid compositions as claimed and the proposed combination set forth by the Examiner would not result in the invention as claimed. Therefore, the rejection as set forth by the Examiner is in error and should be withdrawn.

In addition, Materne et al. is silent as to any suggestion of the use of calcium chloride or other metal ions in the formulation of saturated phospholipids, or the benefit of such materials on the issue of physical (as opposed to chemical) stability. As discussed above, the disclosure in Materne et al. relates to chemical stability of unsaturated phospholipids. Such a teaching in no way suggests the use of calcium or other metal ions with saturated phospholipids or storage stable compositions as currently claimed.

Furthermore, it is quite unexpected that the addition of a very hygroscopic salt such as calcium chloride to a dry powder prone to moisture induced destabilization would provide beneficial stabilization properties to the dry powder. This is described at page 8, lines 7-28 of the specification as filed. As seen at page 9, lines 18-22, the present inventors have observed that the gel to liquid crystal transition temperature of the phospholipid can be manipulated by varying the amount of metal ion in the formulation in order to obtain phospholipid-based dry powders that both flow well and are readily dispersible. This is reflected in the claims which recite that the lipid-metal ion complex comprises sufficient metal ion to result in a particulate having an increased gel to liquid crystal transition temperature compared to formulation lacking the metal ion wherein the powder is storage stable. Such unexpected results are nowhere disclosed or suggested by the combination proposed by the Examiner.

The superiority in physical stability of the powders of the present invention compared to that of powders of Materne et al. is further evidence of the non-obviousness of the present invention. Presented herewith for the Examiner's consideration is the Declaration of Dr. Weers under 37 C.F.R. §1.132 directed to the unexpected results attributed to the present invention. As discussed in detail in the declaration, the beneficial results regarding physical stability resulting from the use of metal ions such as calcium with saturated phospholipids were both superior to and unexpected from the use of such metal ions with unsaturated phospholipids, such as those disclosed in Materne et al.

The claims have been amended to recite the limitation that the powders are storage stable. Storage stability is discussed throughout the specification, for example at page 1, line 14; page 4, lines 10-30; and page 8, lines 7-28, for example. As evidenced in

the enclosed declaration, metal ion complexes with unsaturated phospholipids are not storage stable. As seen in paragraph 4 of the declaration, from a product quality standpoint, the T_g or T_m should be much greater (ca. $t_m - t_s > 50°C$) then the storage temperature (t_s) to ensure good long-term stability. The Tm values for unsaturated phospholipids with and without calcium observed from the experimental results set forth in paragraph 17 of the declaration were found to be less than 10 °C. Thus, the addition of metal ions to unsaturated phospholipids does not result in storage stable powders for pharmaceutical applications.

In addition to the significant increase in Tm of saturated phospholipids due to the addition of metal ions, the present inventors have found that the addition of metal ions to saturated phospholipids maintains these elevated order-to-disorder transition temperatures of the phospholipids constant as a function of water content. This is discussed in paragraph 8 of the attached declaration. The superior physical stability and protection from water provided by the addition of metal ions to saturated phospholipids further illustrates the unexpected results of the present invention.

As discussed above and seen in paragraphs 5 and 6 of the attached declaration, the teachings in Materne et al. are limited to chemical stability associated with unsaturated phospholipids. Paragraphs 10 – 17 of the declaration relate comparative studies performed to examine various physicochemical differences of spray-dried powders comprising unsaturated or saturated phospholipids and calcium chloride as an exemplary metal ion. In particular, paragraphs 14, 15 and 16 present the results of visual, SEM, and DSC analysis. As seen in paragraph 10 of the declaration, the addition of calcium chloride to saturated phospholipids provided a significant increase in the gel to liquid crystal transition temperature, thus improving physical stability of the powders, while also protecting the powders from effects of increases in relative humidity. No such benefit was achieved through the addition of calcium chloride to unsaturated phospholipids since even with calcium, the transition temperatures of unsaturated phospholipids remained well below room temperature and were even below 0 °C.

Thus, for all of the reasons set forth above, Applicants respectfully submit that the rejection has been overcome and should be withdrawn.

Claims 1-32 and 44-52 have been rejected under 35 U.S.C. §103 as being obvious over Weers et al. in view of Materne et al. The Examiner states that it would have been obvious to one of ordinary skill in the art at the time of the invention to substitute the calcium phosphatidylcholine chloride of Materne et al. for the phosphatidylcholine of Weers et al. in view of the teachings in Materne et al. of increased processibility and stability of calcium phosphatidylcholine chloride disclosed in Materne et al.

Applicants respectfully submit that this rejection has been overcome in view of all of the reasons set forth above.

Applicants believe that all of the pending claims are presently in condition for allowance. Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "Version with markings to show changes made".

If it is believed that this will expedite prosecution of the present application, the Examiner is invited to telephone the undersigned attorney at the number below

Respectfully submitted,

Date: 11/25/02

By: _____

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Version with Markings to Show Changes Made

In the Claims

Claims 6 and 7 have been cancelled.

Claims 53-71 are new.

1. A particulate composition for delivery to the pulmonary system comprising:

[hollow and porous] particles comprising a saturated phospholipid and a polyvalent cation in an amount effective to increase the gel-to-liquid crystal transition temperature of the particle compared to particles without the polyvalent cation, wherein the particulate composition is storage stable.

10. A particulate composition according to claim 8 wherein the molar ratio of divalent cation to phospholipid [surfactant] is at least 0.05.

11. A particulate composition according to claim 10 wherein the molar ratio of divalent cation to phospholipid [surfactant] is 0.05 – 2.0.

12. A particulate composition according to claim 10 wherein the molar ratio of divalent cation to phospholipid [surfactant] is 0.25 – 1.0.

14. A particulate composition according to claim 13 wherein the molar ratio of calcium to phospholipid [surfactant] is about 0.50.

16. A particulate composition according to claim 1 further comprising [0.1 – 80% w/w of] an active agent.

17. A particulate composition according to claim 16 wherein the active agent is selected from the group consisting of nicotine, human growth hormone, parathyroid hormone, leuprolide, budesonide, tobramycin, albuterol, insulin, interferon alpha, interferon beta, amphotericin, fluticasone, salmeterol, formoterol, and salts thereof.

31. A particulate composition [for delivery to the pulmonary system] comprising:

[hollow and porous] biodegradable particles comprising a phospholipid and a polyvalent cation wherein the composition comprises a gel-to-liquid transition temperature Tm and a storage temperature Ts wherein Tm > Ts by at least 20 °C.

32. A particulate composition for delivery to the pulmonary system comprising:

20 – 99.9% of a saturated phospholipid;

a polyvalent cation in an amount effective to increase the gel-to-liquid crystal transition temperature of the particle compared to particles without the polyvalent cation; and, optionally

0.1 – 80% active agent;

wherein the composition is in the form of hollow and porous particles.

44. A method for delivery to the pulmonary system comprising administering to the respiratory tract of a patient in need of treatment an effective amount of [hollow and porous] storage stable particles comprising a saturated phospholipid and a polyvalent cation present in an amount effective to increase the gel-to-liquid crystal transition temperature of the particle compared to particles without the polyvalent cation.

52. A method according to claim 51 wherein the particles further comprise an active agent selected from the group consisting of nicotine, human growth hormone, parathyroid hormone, leuprolide, budesonide, tobramycin, albuterol, insulin, interferon alpha, interferon beta, amphotericin, fluticasone, salmeterol, formoterol and salts thereof.